Improving the Lives of Patients with Liver Diseases

Corporate Presentation

November 2019
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CymaBay
Transforming into a fully integrated company

CymaBay
- Focus on improving the lives of patients with inflammatory liver diseases
- Targeting indications with limited or no approved therapies and high unmet need
- Forward integrating into a Commercial organization to prepare for first launch

Seladelpar
- Poised to be the first and only selective PPARδ agonist approved for patients
- Potent PPARδ agonist with pleiotropic regulation of critical liver disease pathways
- Oral once daily dose with advantageous tolerability profile

Value
- Three late-stage development programs reading out in the next 2 years
- Highly de-risked pivotal Phase 3 in Primary Biliary Cholangitis (PBC) with Breakthrough Therapy Designation (BTD)
- Phase 2 initiated in Primary Sclerosing Cholangitis (PSC), a second orphan cholestatic liver disease
- NASH Phase 2b presents upside and strategic options
CymaBay
Delivering on seladelpar to drive value

2019

- NASH Ph 2 Enrolled✓
- PBC Breakthrough Therapy (FDA)✓
- CymaBay Raises $115M✓
- NASH Ph 2 Liver Fat 12 Weeks✓
- PBC Ph 2 First Patient✓
- PBC Ph 3 Readout

2020-21

- PBC NDA Filed
- PSC Ph 2 Readout
- PSC Ph 3 ENHANCE Enrolled
- PBC Ph 3 Readout
- PSC Ph 2 Fully Enrolled
- NASH Ph 2 Histology 52 Weeks
- PBC Ph 2 Readout 52 Weeks
- NASH Ph 2 Liver Fat 12 Weeks✓
Seladelpar

Differentiated opportunity addressing unmet needs in liver disease

1.8 Å RMSD X-ray Crystal Structure
Seladelpar - PPARδ Ligand Binding Domain
EC_{50} = 2nM

First potent and selective PPARδ agonist in development for inflammatory liver diseases

Oral, once daily with clinical activity down to 5 mg and clinical experience with exposures beyond one year

Regulation of pathways important in inflammatory liver diseases; bile acids, lipid metabolism, inflammation and fibrosis
Seladelpar
Targets all important cell types in liver disease

Decrease Bile Acids
- Cholesterol synthesis
- Bile acid synthesis (C4)
- Transport

Anti-Fibrotic
- Connective Tissue Growth Factor
- Stellate cell activation
- Collagen synthesis/deposition

Anti-Inflammatory
- NFκB-dependent gene activation
- Inflammatory cytokines
- hs-C-Reactive Protein

Increase Lipid Metabolism
- Cholesterol/LDL-C
- Fatty acid oxidation
- Insulin sensitivity

Regulates genes that control pathways in liver health and disease
Seladelpar
Primary Biliary Cholangitis

Breakthrough Therapy (FDA) and Priority Medicine (EMA) Designations

Potential to serve the two key unmet needs for patients with PBC – better efficacy and improved tolerability
Primary Biliary Cholangitis
Orphan, autoimmune inflammatory disease of the liver

- Impairment of bile flow (cholestasis), portal inflammation and destruction of bile ducts
- Elevated serum markers of cholestasis including alkaline phosphatase (AP), gamma-glutamyl transferase (GGT) and total bilirubin
- Clinical symptoms of fatigue and pruritus (itching)
- Affects 1 in 1,000 women over 40 (~130,000 patients in the U.S.)

AP below 1.67x the upper limit of normal and normal total bilirubin are clinical surrogates for slowing disease progression
Despite Current Therapies Unmet Need Remains
Patients need improved efficacy and better tolerability

<table>
<thead>
<tr>
<th>Ursodeoxycholic Acid (UDCA) 1st Line</th>
<th>Obeticholic Acid (Ocaliva) 2nd Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>▲ First line therapy for PBC</td>
<td>▲ Add-on therapy for UDCA inadequate responders</td>
</tr>
<tr>
<td>▼ ~40% inadequate responders: AP &gt;1.67x ULN</td>
<td>▲ Monotherapy for UDCA intolerant patients</td>
</tr>
<tr>
<td>▼ Additional 5% are intolerant to therapy</td>
<td>▲ AP/bilirubin as biomarkers for accelerated approval</td>
</tr>
<tr>
<td></td>
<td>▼ ~50% inadequate responders</td>
</tr>
<tr>
<td></td>
<td>▼ Can cause or worsen pruritus</td>
</tr>
</tbody>
</table>

Seladelpar is being developed as a potential improved 2nd line treatment for PBC
Seladelpar Phase 2 Open Label Study in PBC
Add-on for patients with an inadequate response or intolerance to UDCA

**Entry Criteria:**

AP $\geq 1.67\times$ ULN; ALT/AST $\leq 3\times$ ULN; Total Bilirubin $\leq 2\times$ ULN

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**Week 12**

At week 12 a dose adjustment in the 5/10 mg group was made based on patient response and tolerability.

**Week 52**

Patients with AP $\leq 1.67\times$ ULN, $\geq 15\%$ drop in AP from baseline and normal total bilirubin.

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**Primary Outcome:**

$\%$ change in AP from baseline

**Secondary Outcomes:**

composite responder rate, AP normalization, changes in liver, metabolic and inflammatory markers

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1At week 12 a dose adjustment in the 5/10 mg group was made based on patient response and tolerability.
2Patients with AP $\leq 1.67\times$ ULN, $\geq 15\%$ drop in AP from baseline and normal total bilirubin.
Seladelpar Phase 2 Study in PBC

Baseline demographics of mITT population (N=34 at 52 weeks)*

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean (SD)</th>
<th>Seladelpar 5/10 mg (n=17)</th>
<th>Seladelpar 10 mg (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>49 (5)</td>
<td>48 (11)</td>
<td></td>
</tr>
<tr>
<td>Female/male</td>
<td>17/0</td>
<td>16/1</td>
<td></td>
</tr>
<tr>
<td>History of Pruritus, n (%)</td>
<td>11 (65)</td>
<td>14 (82)</td>
<td></td>
</tr>
<tr>
<td>Pruritus VAS (0-100)</td>
<td>19 (22)</td>
<td>37 (31)</td>
<td></td>
</tr>
<tr>
<td>AP (37-116 U/L)</td>
<td>351 (166)</td>
<td>279 (74)</td>
<td></td>
</tr>
<tr>
<td>ALT (6-41 U/L)</td>
<td>41 (17)</td>
<td>52 (25)</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin† (0.10-1.10 mg/dL)</td>
<td>0.56 [0.50, 0.70]</td>
<td>0.75 [0.57, 1.14]</td>
<td></td>
</tr>
<tr>
<td>UDCA Dose, mg/kg/day</td>
<td>15 (4)</td>
<td>17 (3)</td>
<td></td>
</tr>
</tbody>
</table>

*Data as of July 23, 2018 and includes only patients that reached 52-weeks at such date

†Median [Quartiles: 25, 75]. mITT, modified intention to treat; VAS, visual analogue scale.
Seladelpar Phase 2 Study in PBC
Rapid and sustained decrease in AP through week 52

Mean Percent AP Change Baseline to Week 52

Mean AP from Baseline to Week 52

*P<0.0001 for both groups compared to baseline values

Mean ± SEM

Decreases in AP >45% observed at 5/10 mg and 10 mg
Seladelpar Phase 2 Study in PBC
Up to 71% of patients achieved the composite efficacy endpoint

Composite Responder Rate

<table>
<thead>
<tr>
<th>Dose</th>
<th>Responder Rate</th>
</tr>
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<tbody>
<tr>
<td>5/10 mg</td>
<td>59%</td>
</tr>
<tr>
<td>10 mg</td>
<td>71%</td>
</tr>
</tbody>
</table>

AP Normalization

<table>
<thead>
<tr>
<th>Dose</th>
<th>AP Normalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/10 mg</td>
<td>24%</td>
</tr>
<tr>
<td>10 mg</td>
<td>29%</td>
</tr>
</tbody>
</table>
Seladelpar Phase 2 Study in PBC
Average total bilirubin levels stable through week 52

Mean Total Bilirubin

Dose adjustment for 5/10 mg group
Seladelpar Phase 2 Study in PBC
Patient reported pruritus: Treatment not associated with increase

Visual Analog Scale (VAS) through week 52

Median Change in VAS

- Baseline median VAS, 5/10 mg=10 and 10 mg=32
- Dose adjustment for 5/10 mg group
- In patients with baseline itch, the median changes in VAS were -30% and -66% in the 5/10 mg and 10 mg groups, respectively

Median VAS

- Dose adjustment for 5/10 mg group

5/10 mg, n=17
10 mg, n=17
Seladelpar Phase 2 Study in PBC
Significant decreases in transaminase through week 52

*P<0.0001, compared to baseline values
11 serious AEs in the study; none were deemed related to seladelpar

No ≥ grade 3 ALT elevations

Three discontinuations
  - Related: Grade 1 gastroesophageal reflux
  - Unrelated: Pneumonia & worsening of pruritus

No discontinuations for transaminase elevations

Overall, no increase in pruritus

<table>
<thead>
<tr>
<th>AE</th>
<th>5/10 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>22%</td>
<td>18%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13%</td>
<td>7%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14%</td>
<td>6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>14%</td>
<td>6%</td>
</tr>
</tbody>
</table>
Seladelpar for PBC
Significantly de-risked Phase 3 program

Response of up to 71% of patients in registration endpoint

No signal for drug-induced itch

Phase 2 study enrolled with 104 patients beyond 52 weeks

ENHANCE Phase 3 global registration study enrolling
ENHANCE Phase 3 Pivotal Study

Phase 3 study design

- **Primary Outcome:** Composite responder rate (AP <1.67xULN, ≥15% decrease in AP, total bilirubin ≤ULN)

- **Secondary Outcomes:**
  - Proportion of patients with AP ≤1.0xULN at 6 and 12 months
  - Change from baseline in pruritus Numerical Rating Scale using e-diary at 6 months
| Population | Intolerance or inadequate response to UDCA  
AP ≥ 1.67 x ULN, bilirubin ≤ 2 x ULN  
Includes patients with severe pruritus |
|-----------|---------------------------------------------------------------------|
| Design    | Double blind, 52-week, placebo-controlled  
Seladelpar 5/10 mg titration and 10 mg vs. placebo (1:1:1 randomization)  
Stratified by AP and pruritus |
| Primary Outcome | Composite responder rate (AP <1.67xULN, ≥15% decrease in AP, total bilirubin ≤ULN) |
| Secondary Outcomes | Proportion of patients with AP ≤1.0xULN at 6 and 12 months  
Change from baseline in pruritus Numerical Rating Scale using e-diary at 6 months |
Anti-cholestatic and Anti-inflammatory Activities that May Support Potential Treatment Effect in PSC
Primary Sclerosing Cholangitis
Orphan, cholestatic inflammatory disease of the liver

- Characterized by diffuse inflammation and fibrosis of both intra- and extra-hepatic bile ducts
- May progress to end-stage liver disease
- Common initial symptoms are fatigue, abdominal pain and itching (pruritus)
- ~70% of patients have IBD
- Cholangiocarcinoma develops in 8–30% of patients
- Affects men 2:1 (~40,000 patients in the U.S.)

Only effective therapy is liver transplant

Hirschfield, et al; The Lancet, 2013
# Seladelpar PSC 24 -Week Phase 2 study design

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Week 24</th>
</tr>
</thead>
</table>
| **Seladelpar 5 mg PO QD**  
(n=25) |  
**4 Wk Post-Treatment Safety Follow-up Visit** |
| **Seladelpar 10 mg PO QD**  
(n=25) |  
| **Seladelpar 25 mg PO QD**  
(n=25) |  
| **Placebo PO QD**  
(n=25) |  

**Primary Outcome:**  % change in AP from baseline to week 24

**Secondary Outcomes:**  FibroScan, MRCP and other exploratory measures
Potential mechanism that decreases disease drivers of NASH:

- **metabolic load** – reduces bile acids, cholesterol & lipids
- **cell stress and injury** – reverses hepatocellular ballooning
- **inflammation and fibrosis** – lowers macrophages & collagen
Seladelpar for NASH

Potential role for PPARδ agonists in the treatment of NASH

Pathological Progression from NAFLD to NASH

- Steatosis
- Insulin resistance
- Bile acids
- Free Cholesterol
- Lipotoxic lipids

- ER stress/ROS
- Inflammatory mediators

- Activation & recruitment:
  - Kupffer cells
  - Macrophages
  - Neutrophils
- Cell death
- Stellate cell activation

- Extracellular matrix deposition & remodeling

Seladelpar (PPARδ) Pharmacology
Seladelpar Phase 2b Study in NASH
Paired-liver biopsy 52-week study design

Study design meets FDA/EMA guidance criteria to enable a Ph 3 program

- Seladelpar 10 mg PO QD (n=50)
- Seladelpar 20 mg PO QD (n=50)
- Seladelpar 50 mg PO QD (n=50)
- Placebo PO QD (n=25)

Secondary Outcome: Change in Histology at 52 weeks
Seladelpar Phase 2b Study in NASH
Enrolled patients reflective of phase 3 population

Population
- Histologically confirmed NASH at baseline
- Liver fat content (LFC) ≥10% by MRI-PDFF
- F1 to F3, NAS ≥ 4; 1 point in each component
- Includes diabetics and non-diabetics

12-Week Outcome Measures
- 12-week relative change in LFC
- Liver biochemistry: ALT, AST, GGT, AP
- Lipid markers: LDL-C, triglycerides
- Other inflammatory markers: hs-CRP

Other Key Outcome Measures
- Safety and tolerability
- 52-week histological improvement in NAS and fibrosis
- LFC and cT1 by LMS
- Liver stiffness by MRE and Fibroscan
- Biochemical fibrosis markers and Histoindex® quantitative digital pathology

Study blinded and ongoing to 52 weeks
## Seladelpar Phase 2b Study in NASH

**Baseline demographics and patient characteristics (mITT)**

<table>
<thead>
<tr>
<th>Parameter (Mean ± SD)</th>
<th>Placebo (n = 26)</th>
<th>10 mg (n = 50)</th>
<th>20 mg (n = 47)</th>
<th>50 mg (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>54 (10.5)</td>
<td>53 (12.6)</td>
<td>57 (12.0)</td>
<td>53 (11.3)</td>
</tr>
<tr>
<td>Male/Female (%)</td>
<td>30.8/69.2</td>
<td>30.0/70.0</td>
<td>31.9/68.1</td>
<td>33.3/66.7</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>104.4 (19.9)</td>
<td>95.3 (21.6)</td>
<td>100.7 (22.9)</td>
<td>99.9 (19.9)</td>
</tr>
<tr>
<td>MRI-PDFF (%)</td>
<td>22.3 (9.5)</td>
<td>22.0 (7.8)</td>
<td>20.8 (6.1)</td>
<td>20.5 (6.8)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>61.0 (34.7)</td>
<td>60.4 (29.6)</td>
<td>57.4 (26.3)</td>
<td>67.6 (40.2)</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>43.5 (24.5)</td>
<td>45.2 (24.9)</td>
<td>46.0 (21.1)</td>
<td>46.3 (27.9)</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>99.3 (177.5)</td>
<td>84.7 (124.4)</td>
<td>97.4 (80.6)</td>
<td>66.5 (45.2)</td>
</tr>
<tr>
<td>AP (U/L)</td>
<td>82.1 (34.1)</td>
<td>83.9 (25.1)</td>
<td>81.1 (28.0)</td>
<td>76.5 (21.6)</td>
</tr>
<tr>
<td>NAS</td>
<td>5.3 (1.1)</td>
<td>5.2 (1.0)</td>
<td>5.1 (1.0)</td>
<td>5.1 (1.0)</td>
</tr>
<tr>
<td>Fibrosis Stage</td>
<td>2.1 (0.65)</td>
<td>2.1 (0.70)</td>
<td>2.3 (0.72)</td>
<td>2.1 (0.65)</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>114.2 (45.5)</td>
<td>103.8 (33.0)</td>
<td>111.0 (47.6)</td>
<td>106.7 (40.0)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>151.2 (51.3)</td>
<td>166.4 (79.5)</td>
<td>173.4 (72.8)</td>
<td>154.2 (93.8)</td>
</tr>
</tbody>
</table>

mITT = modified intent-to-treat population
Seladelpar Phase 2b Study in NASH
Changes in relative liver fat content by MRI-PDFF at 12 weeks

Comparative Relative Change from Baseline

Proportion of Subjects with > 30% Relative Change from Baseline

Mean Relative Change in LFC (%)

Proportion of Subjects (%)
Seladelpar Phase 2b Study in NASH
Positive changes in absolute and relative ALT over 12 weeks

Change in Relative ALT Over Time

Change in Absolute ALT Over Time

Weeks

Relative ALT (%, SE)
Placebo (n=27)
10 mg (n=53)
20 mg (n=51)
50 mg (n=50)

Absolute ALT (U/L, SE)
Placebo (n=27)
10 mg (n=53)
20 mg (n=51)
50 mg (n=50)
Seladelpar Phase 2b Study in NASH
Positive changes in absolute and relative GGT

**Change in Absolute GGT Over Time**

- **Placebo (n=27)**
- **10 mg (n=53)**
- **20 mg (n=51)**
- **50 mg (n=50)**

**Change in Relative GGT Over Time**

- **Placebo (n=27)**
- **10 mg (n=53)**
- **20 mg (n=51)**
- **50 mg (n=50)**
Seladelpar Phase 2b Study in NASH
Dose dependent decreases in markers of hepatic injury at 12 weeks

<table>
<thead>
<tr>
<th>%, LS Mean (SE)</th>
<th>Placebo (n = 27)</th>
<th>10 mg (n = 53)</th>
<th>20 mg (n = 51)</th>
<th>50 mg (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10 mg (n = 53)</td>
<td>20 mg (n = 51)</td>
<td>50 mg (n = 50)</td>
</tr>
<tr>
<td>ALT</td>
<td>-8.9 (5.1)</td>
<td>-22.9 (3.8)</td>
<td>-32.0 (4.0)</td>
<td>-37.5 (4.0)</td>
</tr>
<tr>
<td></td>
<td>p=0.08</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>AST</td>
<td>-12.9 (5.8)</td>
<td>-11.6 (4.4)</td>
<td>-15.2 (4.5)</td>
<td>-17.3 (4.5)</td>
</tr>
<tr>
<td></td>
<td>p=0.03</td>
<td>p=0.009</td>
<td>p=0.001</td>
<td>p=0.0002</td>
</tr>
<tr>
<td>GGT</td>
<td>-4.5 (4.3)</td>
<td>-28.2 (3.2)</td>
<td>-37.6 (3.3)</td>
<td>-43.1 (3.4)</td>
</tr>
<tr>
<td></td>
<td>p=0.3</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>AP</td>
<td>4.4 (2.9)</td>
<td>-19.1 (2.1)</td>
<td>-25.1 (2.2)</td>
<td>-33.4 (2.2)</td>
</tr>
<tr>
<td></td>
<td>p=0.12</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

ALT, AST, GGT and AP data from safety population; p-values relative to baseline
Seladelpar Phase 2b Study in NASH
Positive changes in lipid and inflammation parameters at 12 weeks

LDL-C, TG and hs-CRP data from safety population
Seladelpar Phase 2b Study in NASH
Additional Pharmacodynamic Measures at Week 12 Interim Analysis

- Dose-dependent decreases of plasma 7α-Hydroxy-4-cholesten-3-one (C4)
  - Inhibition of hepatocellular bile acid synthesis

- Dose-dependent increases in carnitine and short-chain acyl-carnitines
  - Marker of increased lipid metabolism

- No significant effects using the Enhanced Liver Fibrosis (ELF) panel
  - Plasma based biomarkers of fibrosis (use is exploratory in NASH)

- No significant effects were observed in corrected-T1
  - An exploratory MRI method for inflammation associated with NASH

- The study remains blinded until the 52-week liver histology expected in 2Q 2020
Seladelpar Phase 2b NASH Study
Relative Change in C4 from Baseline to Week 12

Inhibition of hepatocellular bile acid synthesis

N = 177
Study remains blinded
Seladellar Phase 2b NASH Study
Relative Changes in Plasma Acyl-Carnitines After 12 Weeks

Markers of increased lipid catabolism

N = 177
Study remains blinded
Majority of treatment emergent adverse events were mild to moderate and deemed unrelated to study drug.

The most common (>5%) treatment emergent adverse events included nausea, constipation, dizziness, headache, gastroesophageal reflux disease and upper abdominal pain.

Two SAEs both deemed unrelated to study drug.

No Grade 3 or greater ALT/AST elevations.
CymaBay Accomplishments and Goals

2019
- Breakthrough Therapy Designation
- 12-week Ph 2b NASH data
  - Initiate Ph 2 PSC study – Q3
  - Complete enrollment of ENHANCE – Q4

2020
- Ph 2 PBC full data – Q1
- 52-week Ph 2b NASH data (histology) – Q2
- Complete 52-week treatment period of ENHANCE – H2

2021
- ENHANCE data – H1
- PSC Ph2 data – H2
- NDA filing PBC – H2

Improving the lives of patients with liver diseases